Fertilo P1 Study: Safety of the Oocyte Maturation System

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1. Introduction

A. Type of Research

This study is a safety evaluation of the Fertilo Oocyte Maturation System, known as Fertilo. Fertilo is an *in vitro* maturation (IVM) product composed of ovarian support cells (OSCs) which are supplemented into the IVM Medium known as MediCult-IVM. The OSCs utilized in Fertilo are produced from a single commercial and clinically compliant source of human induced pluripotent stem cells (hiPSCs). The OSCs, commonly known as granulosa cells, are a well studied ovarian cell type responsible for providing the required developmental niche for quality oocyte maturation. Fertilo is applied exclusively *in vitro*, with no aspect of the product being used beyond the oocyte maturation stage or for any *in vivo* use. Every lot of Fertilo OSCs is manufactured under strict manufacturing best practices, and comprehensively evaluated for conformance, OSC identity and purity, OSC performance and potency, and absence of advantageous human or animal pathogens including viruses, bacteria, and fungi. All Fertilo OSC batches are generated using reagents that are completely animal origin free (AOF) and meeting international fertility product standards for low endotoxin and mouse embryonic assay (MEA) safety. Each Fertilo batch is produced and delivered with a complete certificate of analysis (COA) to demonstrate product conformity according to Quality Management principles. Prior clinical and nonclinical studies of Fertilo have demonstrated it is a safe and effective approach to maturing oocytes and improving their developmental competence for high quality embryo formation. The aim of this study is to evaluate ongoing pregnancy and live birth rates associated with Fertilo application in minimal stimulation fertility treatment. This study is designed as a single arm safety trial.

B. Objectives of Study

The objective of this study is to evaluate the safety of the Fertilo product through evaluation of ongoing pregnancy and live birth outcomes. Fertilo has been assessed in numerous animal model nonclinical studies, including mouse and bovine models, to significantly improve oocyte maturation and embryo formation rates, and yield healthy, normal live births compared to commercially available IVF and IVM controls. In a mouse reproductive toxicology study, Fertilo significantly improved blastocyst formation relative to Medicult-IVM (59.2% versus 40.8%, p = 0.0001, Fisher's Exact Test). Live birth rate of pregnant female mice did not significantly differ between Fertilo and Medicult-IVM or a COS control (25.3% ± 4.9%, 35.7% ± 5.2%, and 33.8% ± 7.3%, p= 0.507, one way ANOVA). No instances of congenital, developmental, or behavioral abnormality were observed in any mouse test group. In a bovine maturation model, Fertilo significantly improved oocyte maturation rate compared to MediCult-IVM (72.6% ± 3.8% versus 55.3% ± 5.3%, p = 0.03, paired t-test). Prior clinical evaluation of Fertilo in humans has established that Fertilo significantly improves oocyte maturation rate over MediCult-IVM in randomized control sibling oocyte trials (68% ± 6.74% versus 43% ± 7.90%, p=0.0349, paired t-test). Notably, in humans, Fertilo was shown to significantly improve euploid day 5 or 6 blastocyst formation rate

compared to commercial IVM controls in randomized control sibling oocyte trials (25% ± 7.47% versus 11% ± 3.82%, $p = 0.0351$, logistic regression). It has been further demonstrated that Fertilo yields embryos with normal epigenetic, genetic, and morphological quality with no significant difference to reference COS controls ($p = 0.7970$, unpaired *t*-test). The minimal stimulation protocol utilized with Fertilo has been utilized and optimized in over 180 patients to date in five clinical study sites globally, with no severe adverse outcomes noted in any patient today.

When undergoing controlled ovarian stimulation (COS) to yield mature oocytes used for fertilization, conventional *in vitro* fertilization (IVF) treatments involve high doses of gonadotropin stimulation, typically 2,000 to 4,000 IU. These high doses of gonadotropins can in some cases result in serious and detrimental health effects for the patient and can contribute to the overall high burden and cost associated with IVF treatment. Recent estimates show that 2-3% of patients suffer from severe ovarian hyperstimulation syndrome (OHSS) and up to 20-30% of patients undergoing traditional COS experience some degree of mild to moderate OHSS (Papanikolaou *et al*., 2006). Technologies that allow for maturation of oocytes outside of the body can be effectively utilized to significantly reduce the gonadotropin dosage used in patients. Multiple clinical and commercial products have shown that effective pairing of minimal stimulation and IVM can yield embryos that result in healthy live births. This reduced gonadotropin usage results in a safer and more affordable IVF treatment for women.

In Gameto's Fertilo program, immature cumulus oocyte complexes (COCs) are cultured with ovarian support cells (OSCs). Fertilo OSC's act as *in vitro* counterparts to *in vivo* granulosa cells, which are found in the follicular milieu. OSCs work to promote a mature or Metaphase II (MII) state through paracrine signaling in coordination with the surrounding cumulus cells. This program is therefore extendable to eggs at developmentally arrested stages such as germinal vesicle (GV) or metaphase I (MI).

In this study, patients will undergo a minimal stimulation regimen of no more than 800 IU of gonadotropins, and immature COCs will be matured using Fertilo. Resulting MII oocytes will be fertilized with the partner's sperm, or, in cases in which the female subject opts for sperm donation, donor sperm, to create embryos for reproductive purposes. These embryos are supervised for fertilization success, embryo development, and embryo quality throughout the culture period. Blastocysts are biopsied for next generation sequencing (NGS) analysis of embryo ploidy, known as pre-implantation genetic testing for aneuploidy (PGT-A) and those of suitable developmental quality are vitrified for later use. A suitable quality euploid blastocyst will then be thawed and used for single embryo transfer (SET) after uterine priming. Patients will then be monitored for biochemical pregnancy, clinical pregnancy, ongoing pregnancy and live birth as well as any associated adverse events.

The primary and secondary objectives are summarized as follows:

Primary Outcome Measure:

Cumulative Live birth rate [Time Frame: At least 24 weeks of gestation up to the time of delivery]
Live birth is defined as the birth of at least one newborn after 24 weeks' gestation that exhibits any sign of life (twin will be a single count). Live birth rate is calculated per embryo transfer and per cycle for each patient (this includes patients with no euploid blastocysts available for transfer). Live birth rate is reported for the study arm as a percentage and absolute number across all patients included.

Secondary Outcome Measures:

IVM and Embryo Outcomes

1. Number of COCs retrieved [Time Frame: within 4 hours of oocyte retrieval]

Defined as the number of COCs containing an oocyte at the time of retrieval. Measured as a total number per patient and as a mean and standard deviation per retrieval for the study arm.

2. MII formation [Time Frame: 30 hours post-oocyte retrieval]

A Metaphase II (MII) oocyte is defined as an oocyte with a first polar body (PB1). MII formation is measured as a total number of MII oocytes and as a percentage for each patient and as a mean and standard deviation for the study arm. Percentage will be calculated relative to the number of COCs for each patient.

3. Fertilization [Time Frame: 16 to 18 hours post-ICSI]

Fertilization is assessed 16 to 18 hours after ICSI by assessment of pronuclei formation. The presence of 2 pronuclei and two polar bodies is considered normally fertilized. Embryos with 1 pronuclei or more than 2 pronuclei will be kept for evaluation, as timing and fragmentation/vacuoles can affect pronuclei visualization without deleterious effect on embryo formation. Embryos with zero pronuclei are considered failed to fertilize. Fertilization will be measured as a total number of fertilized oocytes and as a mean and standard deviation for the study arm. Percentage will be calculated relative to the number of COCs and injected oocytes for each patient.

4. Cell cleavage [Time Frame: 3 Days post-oocyte ICSI]

Cleavage is assessed on day 3 post-ICSI. Embryos with the presence of 2 or more cells are considered to be cleaved. Fertilized embryos displaying a single cell will be considered not cleaved. Cell cleavage is measured as a total number and percentage for each condition and as a mean and standard deviation for the study arm. Percentage will be calculated relative to the number of COCs, MIIs, and fertilized oocytes in condition.

5. Blastocyst formation [Time Frame: Within 7 Days post-oocyte ICSI]

Blastocyst formation is assessed at day 5, 6 and 7 post-ICSI. Embryos that have successfully passed the morula stage, as indicated by cavitation, will be designated as blastocysts. Blastocyst formation is measured as a total number of blastocysts and percentage for each patient and as a

mean and standard deviation for the study arm. Percentage will be calculated relative to the number of COCs, MIIs, and fertilized oocytes in condition.

6. Euploid blastocyst formation rate [Time Frame: Within 7 Days post-oocyte ICSI]

Euploid embryos are determined by PGT-A analysis of trophectoderm biopsies showing no evidence of chromosomal or segmental aneuploidy. The PGT-A laboratory will use next generation sequencing (NGS) with thresholds set to distinguish two categories: euploid vs. aneuploid blastocysts. Low level mosaicism will not be counted as aneuploid. Euploidy will be measured as a total number of blastocysts and as percentages of COCs, MIIs, fertilized oocytes and biopsied blastocysts for each patient and as a mean and standard deviation for the study arm.

7. Blastocyst quality scores [Time Frame: 5-7 Days post-ICSI, scored at time of biopsy]

Quality scores are recorded at the time of assessment for biopsy and vitrification either on Day 5, 6 or 7 post-ICSI. Qualitatively assessed as a score for each individual embryo according to the Gardner Scale. Blastocyst quality scores are assessed individually for each biopsied/vitrified blastocyst.

8. Vitrified blastocyst number [Time Frame: 5-7 days post-ICSI]

Vitrified blastocyst number is determined when blastocysts are vitrified as the number of blastocysts vitrified per patient. The vitrified blastocyst number is expressed as a total number and percentage for each patient and as a mean and standard deviation for the study arm.

Pregnancy Outcomes (following Frozen Embryo Transfer of Euploid Blastocysts)

1. Biochemical pregnancy [Time Frame: 9-10 days after embryo transfer]

The level of hCG in the patient's blood (serum) is determined 9 to 10 days after embryo transfer. A value >5mIU/ml is considered a positive pregnancy test. Measured as a total number and percentage of patients with a positive beta hCG for the study arm. Percentage will be calculated relative to the number of transfers in arm and relative to the number of patients.

2. Clinical pregnancy [Time Frame: At a minimum of 5 to 7 weeks from embryo transfer]

Pregnancy with gestational sac visible with ultrasound at 7 weeks' gestation, reported as a patient with a clinical pregnancy. Reported as a total number of patients with a clinical pregnancy and as a percentage for the study arm. Percentage will be calculated relative to the number of transfers and the number of patients in arm.

3. Early miscarriage [Time Frame: Before 12 weeks of gestation]

Defined as loss of a clinical pregnancy before the 12^{th} week of gestation, reported as a patient N. Measured as a total number and percentage for the study arm. Percentage will be calculated relative to the number of transfers and clinical pregnancies in arm.

4. Ectopic pregnancy [Time Frame: Before 12 weeks of gestation]

Ectopic pregnancy is defined as the implantation of an embryo outside of the uterus. Ectopic pregnancy is reported as a total number of ectopic pregnancies and as a percentage for the study arm. Percentage will be calculated relative to the number of transfers in arm.

5. Ongoing pregnancy [Time Frame: At a minimum of 10-12 weeks from embryo transfer]

An ongoing pregnancy is defined as a fetal sac visualized with ultrasound with detectable fetal heart rate at 10 weeks' gestation, it may include all clinical pregnancies with a beating fetal heart that result in either a live birth or a miscarriage. Ongoing pregnancies are reported as a total number and as a percentage for the study arm. Percentage will be calculated relative to the number of cycles and transfers in arm.

6. Late miscarriage [Time Frame: Between 12–24 weeks of gestation)

Defined as loss of a clinical pregnancy between the 12^{th} and 24^{th} week of gestation, reported as a patient N. Measured as a total number and percentage for the study arm. Percentage will be calculated relative to the number of transfers and clinical pregnancies in arm.

7. Preterm delivery [Time Frame: Between 24 weeks to 37 weeks of gestation]

Measured as birth of a baby, with secondary analysis by time of delivery with three groups: <28 weeks, 28-34 weeks, and 34-37 weeks, reported as a patient N. Measured as a total number and percentage for the study arm. Percentage will be calculated relative to the number of deliveries and/or the number of transfers in arm.

8. Gestational age at delivery [Time Frame: 24 to 42 weeks of gestation]

Gestational age at delivery is defined as the date of the delivery minus the date of the embryo transfer. It may be measured in weeks and will be calculated as an average of weeks with a standard deviation for the group. Measured as a mean and standard deviation for the study arm. Percentage will be calculated relative to the number of transfers in arm.

9. Birth mass [Time Frame: At birth]

Measured in grams at time of birth, with a secondary analysis split between singletons and twins. Measured as a mean and standard deviation for the study arm.

10. Twins/Multiples [Time Frame: At Birth]

Twins and triplets are assumed to have arisen from a single embryo transfer, as only one embryo is transferred at a time in this study. Twins and triplets arising after transfer of a single blastocyst regardless of whether they are monochorionic or multi chorionic are considered monozygotic (identical) twins or triplets. The number of multiple births will be determined and reported as a number of twins and/or triplets and as a percentage for each condition and as a mean and standard deviation for the study arm. Percentage will be calculated relative to the number of live births and/or the number of transfers in arm.

11. Stillbirth [Time Frame: Between 24 weeks to Birth]

Stillbirth is defined as a loss of baby life after 24 weeks of pregnancy before or during birth, reported as a patient N. Measured as a total number and percentage for the study arm. Percentage will be calculated relative to the number of transfers and ongoing pregnancies in arm.

Patient health and adverse events outcomes (during stimulation and after embryo transfer)

1. Ovarian hyperstimulation syndrome (OHSS) [Time Frame: Within 2 weeks of oocyte retrieval]

Evidence of OHSS will be assessed during and after stimulation and categorized as mild, moderate or severe. Grade I (mild) - characterized by ovarian enlargement (ovary size 5 to 7 cm), may be

accompanied by abdominal discomfort of varying degrees. Grade II (moderate) - characterized by distinct ovarian cysts (ovary size 8 to 10 cm), accompanied by abdominal pain and tension, nausea, vomiting, and diarrhea. Grade III (severe) - characterized by enlarged cystic ovaries (ovary size >10 cm), accompanied by ascites and occasionally hydrothorax. In rare cases, Grade III OHSS may be further complicated by the occurrence of thromboembolic events. Outcome will be measured as a frequency across the study arm.

2. General health side effects of stimulation [Time Frame: Within 2 weeks of oocyte retrieval]
General health effects of stimulation will be measured through a patient questionnaire during and after retrieval, specifically the day of oocyte pickup (OPU), 8 to 10 hours after OPU, and two weeks after OPU. Patients will be asked their pain level on a scale of 1-10 and instances of pain medication usage, abdominal swelling and tenderness, nausea or vomiting, breast swelling and tenderness. Outcomes will be measured as a percentage for each side effect measured over the study arm.

3. Complications of Pregnancy [Time Frame: Within 10 months of embryo transfer]
Complications during pregnancy will be assessed by phone questionnaires self reported by the patient. These complications include but are not limited to preeclampsia, hypertension, bleeding, abruption, HELLP, and infections. Outcomes will be measured as a frequency for each adverse event measured over the study arm.

4. Congenital abnormalities [Time Frame: Within 10 months of embryo transfer]
Congenital abnormalities will be assessed by phone questionnaires self reported by the patient. These abnormalities include but are not limited to congenital diabetes, congenital genetic disease, and NICU admission. Outcomes will be measured as a frequency for each adverse event measured over the study arm.

C. Background of the Study

Oocyte maturation rates are a key first obstacle in IVF, as current standards of care are to discard all immature oocytes at the time of retrieval. In minimal stimulation scenarios nearly all oocytes that are retrieved are immature, requiring *in vitro* maturation (IVM). IVM holds promise as a strategy for allowing for a reduced gonadotropin load during traditional IVF, which will significantly improve patient care and safety and affordable access to IVF.

Oocyte maturation is a coordinated nuclear and cytoplasmic process, which results in the extrusion of the first polar body (PB1) and deposition of required proteins and transcripts needed for fertilization competence and embryogenesis. This process is normally completed in the ovary, in response to complex, timed extrinsic signals provided through hormone signaling, growth factor production, and nutrient dynamics in the follicular environment. Decades of research into how oocytes develop have led to the creation of IVM-stimulating cell culture media such as Medicult-IVM and SAGE-IVM, which are commercially available and approved for human oocyte IVM. However, limited systematic studies and high variance in efficacy of Medicult and SAGE have

prevented their widespread adoption. Limited studies have shown that both media do not significantly improve oocyte maturation compared to more common culture media such as TCM-199 and Cleavage media. Both continue to fall short of the maturation achieved *in vivo*. Therefore, new cell culture platforms are needed to improve oocyte maturation rates in a robust and reproducible manner.

In this study, the IVM product known as Fertilo is investigated for its use in yielding quality embryological and gestational outcomes. The Fertilo system is a human induced pluripotent stem cell (hiPSC)-derived ovarian supporting cell (OSC) line, with high functional similarity to *in vivo* granulosa cells. These cells are functionally characterized and qualified during manufacturing and utilized as support cells for developing oocytes in Fertilo. These cells are FSH-tuned steroidogenic and growth factor producing, providing the needed metabolites for robust development of oocytes and cumulus cells. In the Fertilo condition immature COCs and OSCs are co-incubated in a Medicult base media droplet to drive oocyte maturation. These OSCs are then eliminated from culture and the oocytes are washed and then utilized for subsequent fertilization by intracytoplasmic sperm injection (ICSI). Fertilo is an entirely *in vitro* product, and no aspect of Fertilo interacts directly with the patient in an *in vivo* context.

Limited studies into IVM oocytes have demonstrated their developmental capacity for embryo formation. While these studies show a large variation in outcomes, they demonstrate that IVM-assisted oocytes can form healthy, euploid embryos and offspring (Edirisinghe et al. 1997, Liu et al. 2003, Qian et al. 2005, Pham et al. 2022, Vuong et al. 2022). Our clinical studies have demonstrated that oocytes cultured in the presence of Fertilo are able to successfully mature and generate euploid blastocysts at rates superior to commercially available IVM systems. We have likewise demonstrated that embryos produced from Fertilo treatment display normal chromosomal and epigenetic health compared to conventional IVF and IVM embryos. Additionally, multigenerational mouse models of Fertilo have demonstrated Fertilo is safe and generates healthy, fertile animal offspring with no evidence of reproductive or developmental toxicity.

The goal of this study is to establish the clinical safety profile of the Fertilo product through evaluation of embryological and gestational outcomes. Throughout the study, metrics of success will be evaluated at every stage of the patient and gamete treatment process with particular focus on patient health and adverse event outcomes.

1. Participant Selection

A. Exclusion and Inclusion Criteria

INCLUSION CRITERIA:

1. Written informed consent
2. Premenopausal, age 18-37 years at the time of providing informed consent, who is an appropriate candidate for IVF
3. Body Mass Index (BMI) of 21-30 kg/m^2
4. No evidence of hormonal disorders as determined by measurements of thyroid stimulating hormone (TSH), prolactin (PRL), sex hormone binding globulin (SHBG) and total testosterone.
5. Normal uterine cavity as assessed by hysteroscopy, hysterosalpingography or sonohysterography within 2 months of screening
6. Negative and up to date cervical cancer screening (per U.S. Preventive Services Task Force guidelines). All those positive for high-risk human papillomavirus must be negative on subsequent cytology.
7. Presence of both ovaries with no major obstructions (ovarian fibroids, ovarian cysts, high-grade endometriosis)
8. Plan to use one of the resultant embryos within 2 months of egg retrieval
9. Willing and able to take contraceptives
10. Male subjects age of 21-45 years
11. Male subject: provide ejaculated sperm analysis with suitable quality for intracytoplasmic sperm injection (ICSI).These requirements will apply to sperm donors as well.
12. Consent to a study that involves low doses or no doses of gonadotropins followed by retrieval of immature oocytes
13. Willing to have embryos subjected to PGT-A testing

EXCLUSION CRITERIA:

1. Recurrent pregnancy loss (defined as ≥ 2 clinical pregnancies without live birth)
2. AMH < 2 ng/ml
3. Presence of other etiologies (congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome)
4. Contraindications to being pregnant or to any of the IVF hormonal medications to be used in this study
5. Presence of uterine anomaly: mullerian defect (septum, didelphic uterus, bicornuate uterus, unicornuate uterus, arcuate uterus); presence of fibroid(s) affecting the endometrium (myoma, leiomyoma); history of thin endometrium (will not become thicker than 6.9 mm with treatment using exogenous gonadotropins and/or exogenous estrogen); asherman syndrome (intrauterine adhesions)
6. Currently taking: lithium, opioids, and/or thyroid medications (other than for treatment of subclinical hypothyroidism) or other known teratogenic medications
7. Participation in another investigational drug/device trial within previous 30 days of enrollment, or 5 half-lives of the investigational drug, whichever is longer; or planning to participate in an investigational drug/device trial within 30 days of study completion.
8. Greater than 2 previous failed IVF attempts
9. Known history of oocyte maturation defect or cleavage arrest defect
10. Tobacco or nicotine use in the past 12 months
11. History of substance abuse, including alcohol abuse
12. Abnormal, undiagnosed vaginal bleeding at the time of screening

13. Abnormal serum iron, HbA1c, prolactin, Hb levels
14. Any medical or surgical condition that in the Investigator's judgment renders a subject unsuitable for study participation
15. Inability to comply with study procedures
16. Condition that requires PGT-M or PGT-SR
17. Male partner/sperm donor: Known or positive test for high DNA fragmentation in sperm
18. Male partner/sperm donor: requirement for retrograde ejaculation procedures or surgical sperm retrievals

B. Sex

We will recruit patient partners who are genetically XX females and genetically XY males, or subjects who are genetically XX females and wish to perform the procedure with a sperm donor.

C. Race/Ethnic Origin

Gameto aims to include patients of diverse race and ethnic origins, with no exclusion criteria based on race or ethnic origin.

D. Vulnerable Populations

This study does not involve recruitment of Vulnerable Population groups as identified by regulation, such as subjects who are adults unable to consent, children, neonates, prisoners, or pregnant women. However, subjects recruited are expected to become pregnant during the conduct of the study. All subjects will be able to make an informed decision and provide written consent.

E. Age

All female participants in the study are between the ages of 18 to 37. All male participants in the study are between the ages of 21 to 45.

F. Sperm Donors

Sperm will be collected from the clinic's bank or from another certified cryobank, and then transferred to the clinic as a frozen specimen in accordance with clinic standards.

G. Total Number of Participants to be Enrolled

This study is designed as primarily a safety study, aiming to recruit and enroll the minimum number of patients required for analysis of the primary endpoint. The statistical analysis used in this study is primarily descriptive, aimed at evaluating the outcomes and variance across patients for each endpoint. As such, 40 patients total are expected to be enrolled, with 20 enrolled in the multi-center observational phase and 20 enrolled in the randomized control trial phase (10 per arm).

2. Study Design

A. Experimental Procedure Summary

1. **Phase 1: Single arm.**

Intervention Arm: Fertilo; 20 patients; Immature cumulus-oocyte complexes (COCs) are cultured in the Fertilo co-culture condition then fertilized, grown to the blastocyst stage, vitrified, and later transferred for reproductive purpose. This phase of the study will occur in two centers, in Peru and Mexico.

Intervention Treatment: Fertilo OSCs are seeded to a pre-gassed 100µl droplet 1-2 hours before oocyte retrieval in a culture dish under oil. The IVM droplet contains Medicult base media with 10mg/ml human serum albumin (HSA), 500ng/ml androstenedione, 75mIU/ml rFSH, and 100mIU/ml hCG. Immature COCs are plated into a culture dish at ≤10 COCs/droplet. COCs are first transferred through a wash droplet then moved to the final 100µl Fertilo droplet containing the Fertilo OSCs and cultured 30 hours at 37C, a CO2 % achieving 7.2-7.4 pH and 5% O2 under oil. COCs are enzymatically and mechanically stripped and washed of all cumulus and Fertilo OSCs. MII oocytes are then fertilized via intracytoplasmic sperm injection (ICSI) and grown in group culture to the blastocyst stage in Global Total One Step Medium. Blastocysts are then biopsied for preimplantation genetic testing for aneuploidy (PGT-A) and vitrified. The highest quality, euploid embryo is then thawed and used for transfer to patients after uterine priming. A single embryo is transferred at a time for all patients. Implantation rate, clinical pregnancy rate, miscarriage rate, live birth rate, and adverse event rates are measured.

2. **Phase 2: Comparative evaluation.**

Intervention Arm: Fertilo and Medicult-IVM; 20 patients.
Patient randomization to Fertilo or Medicult will occur at trigger day during the ovarian stimulation, with 1:1 alternating allocation. This phase of the study will be performed only at a single center in Peru.

All COCs will be cultured in either Medicult-IVM or Fertilo for 30 hours. Then fertilized, grown to the blastocyst stage, vitrified, and later transferred for reproductive purpose.

Intervention Treatment:
For the Fertilo-IVM arm, OSCs are seeded to a pre-gassed 100µl droplet 1-2 hours before oocyte retrieval in a culture dish under oil. The media for IVM contains Medicult base media with 10mg/ml human serum albumin (HSA), 500ng/ml androstenedione, 75mIU/ml rFSH, and 100mIU/ml hCG. Immature COCs are plated into a culture dish at ≤10 COCs/droplet.

For the Medicult intervention, a 100µl droplet is prepared of IVM medium consisting of Medicult IVM base medium, 10mg/ml human serum albumin (HSA), 75mIU/ml rFSH, and 100mIU/ml hCG.

COCs are first transferred through a wash droplet then moved to the final 100µl Fertilo or Medicult-IVM droplet depending on the experimental arm and cultured 30 hours at 37ºC, a CO2 % achieving 7.2-7.4 pH and 5% O2 under oil. COCs are enzymatically and mechanically stripped and washed of all cumulus, and Fertilo OSCs in the Fertilo-IVM arm. MII oocytes are then fertilized by ICSI and grown in group culture to the blastocyst stage in Global Total One Step Medium. Blastocysts are then biopsied for preimplantation genetic testing for aneuploidy (PGT-A) and vitrified. The highest quality, euploid embryo is then thawed and used for transfer to patients after uterine priming. A single embryo is transferred at a time for all patients. Implantation rate, clinical pregnancy rate, miscarriage rate, live birth rate, and adverse event rates are measured.

B. Experimental procedures for both the single arm and the comparative evaluation

Patient screening, stimulation, and gamete retrieval
In the present study, subjects will be screened under informed consent for inclusion and exclusion criteria through blood testing, general medical evaluation, and ultrasound (for female participants) and semen analysis (for male participants). In order to be included in the study, both the female and male partner pair must meet all inclusion criteria.

Female participants may undergo no less than 7 days and no more than 21 days of oral contraceptive pill (OCP) use prior to initiation of stimulation. This will help achieve a downregulated and more uniform patient response to stimulation, clear any atretic follicles, and to allow for timed retrieval programming. For stimulation, female participants undergo clomiphene and up to 3 doses of FSH (150 UI rFSH/day). Starting the day of first stimulation, careful ultrasound will be performed for each day of stimulation. Specifically, follicle count and follicle size will be monitored and recorded to track stimulation response. Further, blood samples will be collected from the patient on the day of stimulation start, the day of hCG trigger, and the day of oocyte pick up (OPU) to measure serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P4), and estradiol (E2). Serum hormone levels will be utilized to monitor follicle response, avoid premature luteinization during stimulation, and inform future study designs, which is required for contextualizing embryology outcomes and improving stimulation success.

If required, patients may be pre-treated for vitamin D deficiency or insulin resistance using calcifediol or metformin respectively before beginning stimulation. For evaluative purposes, the final day of the washout period is considered Day 1 of the menstrual cycle. On Day 2, transvaginal ultrasound (TVU) will be performed to assess the antral follicle count (AFC) and follicle diameter

for monitoring; in addition, baseline evaluation of serum levels of E2, P4, LH, and FSH will be performed via a local laboratory. On Day 2, controlled ovarian stimulation (COS) begins via administration of 100 mg clomiphene citrate (Clomid) once daily for 5 days (Day 2-Day 6). Ultrasound will be performed on Day 7 to determine the number of 150 IU rFSH (Gonal-F) injections that will be administered. If the leading follicle is 6 mm or less, three once daily injections of rFSH will be administered on Days 7, 8, and 9. If follicles are 7 mm to 9 mm on Day 7, 150 IU (Gonal-F) will be administered once daily on Day 7 and 8, for a total of two injections. If the leading follicle is greater than 9 mm on Day 7, a single injection of 150 IU (Gonal-F) will be administered on Day 7.

The ideal leading follicle diameter range is 10-12 mm. On Day 8, 9 or 10, a recombinant hCG (Ovidrel) trigger of 250 μg will be administered and the oocyte retrieval (OR) will be scheduled for 34-36 hours later. In the event of rapid follicular growth, if a follicle is 13 mm or greater at the Day 2 or Day 7 ultrasound, the cycle will be cancelled and repeated in a subsequent menstrual cycle.

On the day of OPU, serum hormone levels will be evaluated as described above. A final measurement of all follicle sizes and numbers will be performed and recorded. Follicular aspiration will be performed under conscious sedation according to standard clinical guidelines. A 17-gauge single lumen needle will be utilized for follicle retrieval. All visualizable follicles will be punctured for extraction when possible. A suction pressure of 70mm Hg will be used for all retrievals. Frequent needle rotation, known as curettage, will be performed to assist in small follicle extraction. Oocyte aspiration will be performed with Vitrolife ASP medium into warmed collection tubes. Due to potential clotting in the needle, frequent needle flushing will be performed. No follicular flushing will be performed during aspiration. Follicular aspirate will be transferred through an upside down 70-micron filter to separate COCs from blood. The filter will then be turned over atop a dish containing Vitrolife ASP search medium and washed briefly to allow release of COCs into the search medium. Compact COCs will then be identified under stereomicroscope and transferred to a 1ml HEPES buffered holding droplet until all COCs have been identified and isolated. Two embryologists will perform successive searches of fluid to ensure all compact COCs have been identified. All searching will occur on a heated surface, with sufficient speed to ensure minimal disruption of COC quality.

Once all COCs have been identified, the COCs will be manually cleaned of excess tissue to ensure a more uniform cohort then imaged for records as a group. The number of COCs collected will be recorded for endpoint analysis.

IVM and embryological procedures

For *in vitro* culture, a single plate is prepared the day before oocyte retrieval to allow for media and oil equilibration. GPS Universal dishes or BIRR 4+ 8 dishes are utilized for culturing. For the Fertilo intervention, a 100µl droplet is prepared of IVM medium consisting of Medicult IVM base medium, 10mg/ml human serum albumin (HSA), 500ng/ml androstenedione, 75mIU/ml rFSH, and 100mIU/ml hCG. For the Medicult intervention, a 100µl droplet is prepared of IVM medium consisting of Medicult IVM base medium, 10mg/ml human serum albumin (HSA), 75mIU/ml rFSH, and 100mIU/ml hCG. An additional two 50µl droplets are prepared of Medicult base media for wash droplets. More 100µl droplets may be prepared if more than 10 COCs are expected for the retrieval. These droplets are overlaid with IVF-grade oil. An additional 500µl of complete IVM medium is placed into the incubator to gas. Plates are incubated at 37C, a CO2 % that achieves 7.2-7.4 pH, and 5% O2.

For the IVM in Fertilo, 1-2 hours before oocyte culture, Fertilo OSCs are seeded to the culture droplet. Briefly, Fertilo cryovials are thawed for 2 minutes at 37C in a heated bead or water bath. Cells are gently resuspended in 400 µl of pre-warmed IVM medium, added in a dropwise fashion, and transferred to 6.5ml of IVM media and centrifuged at 300 x g for 5 minutes. Supernatant is gently aspirated. After the wash, the Fertilo OSCs are resuspended according to a lot # specific value, provided on the COA, to bring the cells to a concentration of ~2000 cells/µl using the pre-gassed IVM medium. A manual cell count is performed using a hemocytometer to determine the exact concentration of live viable cells. In the Fertilo plate, IVM medium is removed from the droplet and replaced with Fertilo cell suspension according to the cell count to enable 100,000 OSCs per 100 µl droplet. Pipetting is minimized to prevent major loss of equilibration of the droplet, and the Fertilo droplet is again allowed to equilibrate for 1-2 hours prior to COC culturing.

After retrieval and isolation, all COCs are placed directly into the IVM culture droplets. No more than 5 COCs are cultured per droplet. Extra COCs should be placed into additional droplets. COCs are first moved through the wash droplets then moved to the IVM conditions, with minimal transfer of media. COCs are then cultured in the IVM condition for 30 hours. A post-ICSI plate is prepared with 100µl droplets of Global Total media and oil overlay for culture after oocyte fertilization. Plates are incubated at 37C, a CO2 % that achieves 7.2-7.4 pH, and 5% O2. For the control IVM arm, all procedures are performed identically except that no Fertilo OSCs are added to the droplet.

After IVM culture, COCs are denuded through hyaluronidase briefly and mechanically stripped further to remove all cumulus cells and any residual Fertilo OSCs and held in the wash droplets until all oocytes are denuded. Stripped oocytes are then washed through serial dilution three additional times. The number of MII, MI, and GV oocytes in the group is measured and recorded. A group image is taken for record keeping. Oocytes identified as MII are fertilized using ICSI immediately after stripping. All immature oocytes are discarded.

Sperm is procured from male partner or from a pre-specified donor and transferred as a fresh or frozen specimen and prepared for intracytoplasmic sperm injection (ICSI). All male participants will submit a sperm specimen for cryopreservation at least one week in advance of oocyte pick up, to be used in the event fresh sperm procurement does not yield quality gametes. On the day of ICSI, male participants will provide a fresh sperm sample for use. Sperm quality will be measured and recorded at the time of sperm processing and high quality sperm will be used for injection according to normal grading criteria. In the case of a sperm donor, these studies would be performed at the time of collection and storage following the standard clinic or sperm bank procedures for processing.

All mature oocytes are injected with sperm according to standard ICSI procedures. All embryo culture is performed in Global Total One Step Medium. Injected oocytes are then placed in group culture overnight in Global Total media droplets under oil overlay at 37C, a CO2 % achieving 7.2-7.4 pH, and 5% O2. Injected oocytes are imaged and assessed for fertilization success 16-18 hours after injection, based on the presence of two pronuclei. Oocytes that show 0PN are discarded. Oocytes with 1PN or 3+ PN are transferred to separate culture droplets from the 2PN oocytes for monitoring. Embryos are then allowed to grow undisturbed until day 3 post-ICSI. At Day 3 post-ICSI, embryos are imaged and assessed for cleavage, noted by the presence of two or more cells. Embryos that fail to cleave are discarded. Embryos that successfully cleave are hatched through laser assisted zona perforation, using standard procedures. Hatched embryos are then allowed to grow undisturbed until day 5 post-ICSI. Embryos are assessed, imaged, and scored each at day 5, 6, and/or 7 for blastocyst formation and quality. Once a blastocyst is scored as freezable quality (3CC or greater based on the Gardner Scale), trophectoderm biopsy is performed on day 5 or 6 or 7 when the trophectoderm has protruded through the perforation in the zona pellucida. Any embryos failing to reach freezable quality by Day 7 post-ICSI are discarded. Biopsied embryos are then vitrified using the Kitazato protocol and trophectoderm biopsy samples are shipped on ice for PGT-A analysis.

The highest quality, euploid embryo is subsequently thawed using the Kitazato method and used for transfer. Further embryos may be thawed and used for transfer if the first transfer fails to result in successful live birth. Only single embryo transfers of blastocyst stage embryos will be used in this study, and all embryos will be frozen before transfer with no fresh transfers.

Pre-implantation genetic testing for aneuploidy (PGT-A) is performed on all biopsies using next generation sequencing (NGS). Library preparation is performed on site at Sequencing Provider and sequenced via targeted NGS. Clinical reports are given genome-wide for copy number variation (CNV) and single nucleotide polymorphisms (SNPs) to determine the rates of full chromosome aneuploidy or polyploidy as well as segmental aneuploidy and polyploidy. Low level mosaicism is not be considered for ploidy determination in this study.

Only euploid embryos will be transferred for this study. Day 5 embryos will be preferred for transfer over Day 6, and Day 7 embryos will only be transferred if no Day 5 or 6 embryos are available. The highest graded embryo using the Gardner scale will be used for transfer if multiple embryos are available. Additional embryos may be transferred if the first transfer fails to achieve a live birth.

Endometrial priming and embryo transfer

No fresh embryo transfers or transfer of more than one embryo at a time will occur for this study. Endometrial preparation is performed according to the clinical practice standard at the site, using a combination of oral and transdermal estradiol as well as intravaginal and intramuscular progesterone. All transfer cycles will be performed using HRT.

For this study, critical measurements of the gestational process are monitored for success and adverse outcomes including, positive beta hCG rate, implantation rate and clinical pregnancy (measured via presence of gestational sac at 7 weeks). Pregnancy rate prior to 12 weeks will be measured and an ongoing pregnancy rate will be determined via measurement of a detectable heart rate at 12 weeks' gestation. Clinical miscarriage, stillbirth, and preterm delivery rates will be determined. Rates of singletons, twins, gestational age at delivery, live birth rate and birth weight will be determined to complete the study.

Safety of the ART (Assisted Reproductive Technology)

Safety is monitored at each clinic visit or, if any side effects occur, by questioning and examining the patient, with adverse events and serious adverse events recorded on case report forms. Adverse events are defined as any unexpected medical occurrence (symptoms or signs, abnormal laboratory findings or diseases) that emerge or worsen during the trial, relative to the initial trial visit. Possible adverse events including OHSS, ovarian torsion, infection, ectopic pregnancy, miscarriage, medication-related reactions such as overdose, sensitivity and toxicity, and any adverse outcomes related to egg collection. Serious adverse events are defined as any unexpected medical occurrence that resulted in death, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacitation. A congenital anomaly or birth defect is considered a serious adverse event.

B. Analysis of the Study Results

Statistical Analysis of Above Results:

Statistical methods for the study are primarily descriptive, in order to establish frequency rates of the primary and secondary objectives. Data will be compared to historical precedents and to site-specific outcomes to contextualize findings. Rate data is measured and aggregated as a mean and standard deviation for measurements whose distribution is considered normal. Per patient

significance of formation rates (M2, Cleavage, Euploid) will be investigated using Linear Regression analysis using treatment and patient dependent categorical values measured against historical and site-specific controls not generated in this study.

For the comparative evaluation phase, outcomes of both arms will be compared at the interim analysis point, considered completion of the first treatment cycle for all 20 patients. Logistic regression comparing embryo outcomes will be utilized, along with unpaired t-test. It is expected that no less than 65 oocytes per arm are needed for adequate power to detect a rate difference at the oocyte maturation and blastocyst formation stage.

C. Monitoring

All patients will be monitored for adverse health outcomes during the stimulation protocols. We ask that participants self-report any adverse symptoms within two weeks after retrieval. Participants will be given a questionnaire during stimulation and questionnaires after the last retrieval. All patients will be additionally monitored for adverse outcomes during gestation and at live birth through follow ups at pregnancy checks and by phone questionnaires beyond the ongoing pregnancy determination.

D. Storage of Data

All identifiable medical information of the participant will be stored on clinical servers under regulatory-compliant protections provided by the clinic. All data shared with the sponsor will be de-identified patient data and sample data, managed under a Study ID code linked to the patient identifier code. The Sponsor will not have access to identifying information of the patient. All de-identified data will be transferred and stored on Sponsor servers and held for a period of 10 years.

E. Confidentiality of Data

All data will be handled with strict adherence to confidentiality. No identifiable form of information or sequencing will be published or provided to collaborators or journals, except for participants that decide to take part on the optional interview about their participation in the study. In case participants want to take part of the interview, participants will sign a separate consent on the use of their name and likeness to be shared with third parties for the promotion of the study and the Fertilo product.

F. Optional interviews

Participants will have the option to be interviewed about their experience. These interviews will be conducted with the presence of clinic personnel. Participants will be able to take part of the interview, independently from the study. Refusal to participate in an interview will not negatively impact a participant's involvement in the study or any of the other study-related procedures. Those

participants that decide to share their experience anonymously will receive a 50 US dollar value gift card. Those participants that decide to share their experience consenting to the use of their name and likeness in relation to the interview, will receive a 100 US dollar value gift card. The consent to use name and likeness is attached to this filing.

3. Risk/Benefit Assessment

A. Risks

The risks associated with this study are similar to those of IVF treatments. However, for the minimal stimulation protocol, the use of reduced hormonal stimulation is expected to decrease the side effects of the stimulation cycles.

The risks associated with the hormonal stimulation are:

- Ovarian Hyperstimulation Syndrome: The gonadotropin hormones used in the stimulation protocols are known to have, or suspected of having a variety of side effects. The most serious is ovarian hyperstimulation syndrome (OHSS). Its symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, kidney and liver problems, and in the most severe cases, blood clots, kidney failure, or death.
- Ovarian Torsion: Ovarian Torsion is a rare condition when the ovary, and sometimes portions of the fallopian tube, twist around the ligaments that hold it in place. This can cut off the blood flow to the ovary and fallopian tube. If the blood supply is cut off long enough, it could lead to a loss of tissue and of the ovary. The symptoms of ovarian torsion include fever, severe lower abdominal/pelvic pain, cramping, nausea, and vomiting.

These risks, though rare, are expected to be lower in the minimal stimulation protocol utilized versus conventional treatment, as the dosage of hormones administered to participants is reduced.

The risks associated with the egg retrieval procedure are:

- Bleeding: The needle passes through the vaginal wall and into the ovary to obtain the eggs. Small amounts of blood loss are common during egg retrievals. Major bleeding, although very rare, will frequently require surgical repair and possibly loss of the ovary. The need for blood transfusion is rare.
- Anesthesia: For egg retrieval, medications are administered by an anesthesiologist to ease discomfort. Anesthesia such as conscious sedation induced by propofol may be used.

- Infection: Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries or other intra-abdominal organs. Treatment of infections could require the use of antibiotics. Severe infections occasionally require surgery to remove infected tissue.
- Trauma: Despite the use of ultrasound guidance, it is possible to damage other intra-abdominal organs during the egg retrieval. However, the risk of such trauma is low.

The risks associated with pregnancy and delivery are common to IVF and natural reproduction. These risks include:

- Pregnancy complications such as intrauterine fetal demise, preterm labor, preeclampsia, hypertension, HELLP, bleeding or abruption, and general complications during labor
- General risks to the fetus include gestational diabetes, low birth weight, NICU admission, or general congenital abnormality.

B. Prevention of Risks

Before the study, the patient will receive oral and written information about the design, the purposes of the study, and the possible risks that may arise from it. If they subsequently agree to participate, they will sign the informed consent form. They will be able to revoke it and leave the study at any time and for any reason. Participants will be instructed regarding the need to follow the investigators' instructions strictly. Participants will be informed of the need to contact the investigators if an incident arises during the study.

At each medical appointment, the patient will be asked about the adverse effects that may derive from the stimulation, in order to identify and solve them at an early stage. Any participants experiencing severe side effects will be withdrawn from the study, as is standard practice in IVF.

To prevent the serious side effects associated with OHSS the clinic will instruct participants to follow up and report adverse symptoms two weeks after retrieval in each stimulation cycle.

C. Adverse Effects

Adverse effects may occur due to the medication used for hormonal stimulation. Among the most frequent are:

- Headache
- Mood swings
- Difficulty sleeping
- Breast pain
- Pelvic pain

However, for the minimal stimulation experimental protocol that employs minimal hormone doses, these effects will be diminished compared to a standard stimulation protocol.

D. Benefits

Patients undergoing fertility treatment will benefit from the study by receiving the treatment at no cost. They will also benefit as the oocyte maturation treatment under study requires a significantly smaller dose of hormones compared to standard IVF and thus has a safer side effect profile up to oocyte retrieval. There is no additional direct benefit to the study participants.

4. Recruitment and Informed Consent

A. Recruiting

a. General Recruitment

Gameto will not collect health information from interested persons and will not screen the potential participants. The clinic Pranor will recruit and screen the participants to confirm eligibility. Gameto will not pay referral fees for identifying or referring interested participants.

B. Informed Consent

The Informed Consent Form is attached to the materials submitted along with this protocol.

C. Obtaining and Documenting Consent

The consent will be obtained by the Investigator or a member of their team, directly from the participants before that subject takes part in the study. The consent may be documented either with a handwritten signature on paper or through an electronic signature following the Guidance on Use of Electronic Informed Consent, at the participant's option. Participants will receive a copy of the Informed Consent Form.

D. Participant Comprehension and Capability

This research will only involve adult subjects that are able to consent.

E. Costs to Participants

Participants will not bear the costs of any study-related procedures.

F. Compensation to Participants

There will not be any monetary compensation to participants for enrolling in this study. Gameto will cover all costs associated with obtaining and utilizing all gametes and embryos in the study up to three months, for the exclusive ownership and use of the participant. The participant will cover the cost of storing additional vitrified embryos not used directly in the study. Participants will have the option to take part anonymously in an interview about their participation in the study, receiving a fifty US dollar value (USD 50) gift card. Participants will have the option to take part in an interview about their participation in the study, including consenting to the use of their likeness, receiving a one hundred US dollar value (USD 100) gift card.

5. Regulatory, ethical, and trial oversight

5.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol and any amendments, good clinical practice (GCP), and applicable regulatory requirements. This study is to be performed under IRB for the work performed in the study center in Lima, Peru (Pranor clinic). While the products under investigation (Fertilo and MediCult IVM) are available for commercial use in Peru, the nature of the randomization phase of the study warrants IRB approval. This study will not be performed under IRB at the center in Mexico, as the product is available for commercial and clinical use and is only used in the observational portion (phase 1) of the intended study. The study center in Mexico will not participate in the randomization portion of the study.

6. Risk management and quality assurance

6.1. Data Quality Assurance

The Investigator is responsible for ensuring that the clinical data required by the study protocol are carefully reported in the eCRFs. The data entered in the eCRF (in English language) must also be present in the source documents of the subject at the investigational site. As part of the study, all cycle sheets will be collected.

A statement will be signed by the Investigator to confirm that he/she is aware to act under electronic signature, that is, he/she is aware that all the collected data are under his/her responsibility.

All study documentation and results may be reviewed by the Quality Assurance Unit of Gameto/CRO and/or local and foreign Regulatory Authorities. The Investigator accepts herewith to give access to the facilities and to the source data upon request. The Investigator must also permit trial monitoring, audits, IRB review or regulatory inspections.

6.2. Electronic Case Report Form

An eCRF system provided by an independent third party contract research organization will be used for data capture. Trial data should be entered into the eCRF in a timely manner. The timeframe will be specified in the investigator agreement as well as the eCRF guidelines. The investigator will approve/authorize the eCRF entries for each subject with an electronic signature that is equivalent to a handwritten signature.

6.3. Source Data

The Investigator must retain adequate records to include adequate and accurate source documentation of all observations and other data pertinent to the investigation on each subject in the study. These records are to include the eCRFs, source documentation and supporting data, including signed and dated informed consent forms and medical records as well as all cycle sheets.

Source data includes: all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial are source data.

The subject file is a specific file for each subject composed at least by the following source documents:

- Subject's full name, date of birth, weight and height
- Original signed and dated informed consent
- Patient charts and progress notes
- Medical and infertility history
- Demographic data
- Laboratory reports
- Concomitant Medications (Previous and current medications)
- Hospital records

The following trial specific source data items have to be collected in the subject's file as outlined and defined in the monitoring manual produced for this study.

- Study protocol code
- Inclusion/Exclusion Criteria
- Subject's identification code
- Date of inclusion/randomization
- Date of the visits
- IMP accountability and administration
- Occurrence of any AEs/SAEs (including description and duration)
- Embryo Transfer Data sheet and all cycle sheets

- Any assessment or procedure performed (including TVU, US scans and serum pregnancy results) including second trimester pregnancy ultrasound
- Any concomitant therapy
- Status of the subject at the end of trial including pregnancy outcome and newborn exam report
- Reason for discontinuation/withdrawal, if applicable.

7. Discontinuation of intervention and subject withdrawal

7.1. Discontinuation of Trial Intervention

7.1.1. Criteria for Permanent Discontinuation of Trial Intervention

Gameto, as the Sponsor, has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns (e.g. side effect profile not matching expectations; altered risk/benefit ratio), or if completing the trial is no longer practicable (e.g. insufficient enrollment; change in the practice/manufacturing of the Investigational Product, loss of interest). If such action is taken, the reasons for terminating the trial will be documented in detail. All trial subjects still under treatment at the time of termination will undergo a final examination which will be documented.

Gameto, as Sponsor, will submit notification of premature termination or temporary halt to the study sites, IRB providing justification for the decision.

7.2. Subject Withdrawal from the Trial

Participation may be discontinued for any of the following reasons:

- Voluntary subject withdrawal for any reason (the Investigator will seek to obtain the reason and record this in the source documents and eCRF);
- At the Investigator's discretion (the reason should be discussed with Gameto prior to discontinuation and fully documented in the source documents and eCRF);
- If an adverse event (including onset/worsening of concomitant illness) develops, which is considered by the Investigator as incompatible with the continuation of the study;
- If the administration of a drug which is not permitted according to the exclusion criteria is necessary (this should be discussed between the Investigator and Gameto);
- Failure to comply with the requirements of the protocol or significant protocol deviation (e.g. inclusion error, evidence of incompliance with exclusion/inclusion criteria arisen during the study, subject misses study visits)
- If the embryo transfer is not performed, due to not viable blastocysts available after thawing or for other reason (to be specified);
- Lost to follow-up;

- Subject death.

Withdrawn subjects will not be replaced.

7.3. Lost to Follow-Up

A subject will be considered lost to follow-up if she fails to return for the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the Subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the Subject's medical record and study file.
- Should the subject continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4. Trial Stopping Rules

A temporary or permanent cessation of enrollment will be discussed and considered if the following occurs:

SAE or death assessed by the investigator as anything other than unrelated. After a comprehensive safety analysis, the medical review board will recommend whether the study should be resumed without modification, resumed with risk mitigation provisions incorporated into an amended protocol, or stopped. The final decision will be made by Gameto. In the event that the study pausing criteria are triggered the study sites, IRB will be notified immediately.

8. TRIAL ASSESSMENTS AND PROCEDURES

8.1. Study Visit Schedule/Procedures

Screening	Informed consent Medical/IVF history Concomitant medications Local laboratory (hormones, safety) Transvaginal ultrasound Dispense OCPs when qualified
Stimulation (Start of treatment Day 2 and Day 7) No later than 90 days from the screening visit	Concomitant medications Adverse events OHSS evaluation Transvaginal ultrasound Local laboratory (hormones)
hCG Trigger/Randomization	Concomitant medications Adverse events OHSS evaluation Local laboratory (hormones) Randomize subject
Oocyte Retrieval	Concomitant medications Adverse events OHSS evaluation Oocyte retrieval
30 hours post OR	Laboratory only
IVM-ICSI	Laboratory only
16-18 hours post ICSI/Fertilization	Laboratory only
Day 3	Laboratory only
Day 5	Laboratory only
Day 6-7 (if applicable)	Laboratory only
FET prep (uterine priming) No later than 60 days from date of Randomization	Concomitant medications Adverse events OHSS evaluation Transvaginal ultrasound – standard of care Local laboratory (hormones) – standard of care

FET	Concomitant medications Adverse events OHSS evaluation Embryo transfer
Serum hCG (10-14 days post FET)	Concomitant medications Adverse events OHSS evaluation Serum hCG
4-6 weeks gestation	Concomitant medications Adverse events OHSS evaluation Transvaginal ultrasound NIPT
12 weeks gestation or later	Concomitant medications Adverse events OHSS evaluation Transvaginal ultrasound NIPT (if not done earlier)
20-24 weeks gestation	Pregnancy data obtained from OBGYN Anomaly Scan Adverse events of special interest Adverse events Concomitant medications
Phone call live birth up to 6 weeks postpartum	Pregnancy data Birth data Newborn exam report from pediatrician Adverse events of special interest Adverse events

IVF = *in vitro* fertilization; OCP = oral contraceptive pill; OHSS = ovarian hyperstimulation syndrome; hCG = human chorionic gonadotropin; IVM = *in vitro* maturation; ICSI = intracytoplasmic sperm injection; OR = oocyte retrevial; FET = frozen embryo transfer

8.2. Screening/Baseline Assessments and Procedures

8.2.1. Medical/infertility history

A complete medical and infertility history for the female subject will be performed and the results recorded in the subjects' medical record and the eCRF.

Demographic data will be collected at the Screening Visit, including date of birth, gender, race, ethnicity, weight and BMI.

Information on relevant previous and concomitant illnesses, surgeries, or any clinically significant signs or symptoms discovered as a result of screening procedures will be recorded as medical history.

8.2.2. Local laboratory assessments

In order to ensure that the subjects are good candidates for infertility treatment, routine and hormonal laboratory assessments are performed as part of standard of care. These laboratory assessments will be obtained or performed, and recorded in the subjects' charts and in the eCRF.

Serum chemistry and hematology panels with 6 months of screening

Serum FSH, PRL, TSH, LH, P4 and βhCG levels at baseline. For E2 on Day 2, Day 7, and Day 8 or 9

Hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV) antibody, and rubella antibody levels

ABO blood grouping and Rho (D) typing

8.2.3. Transvaginal Ultrasound

Transvaginal ultrasounds (providing imaging of ovaries, uterus, and adnexa, and measurement of follicles and endometrial lining) will be performed according to the study center's standard practice throughout the study and copies of the results filed in the subject chart and entered in the eCRF. AFC will be documented at screening or within 3 months of Screening Visit 1.

8.2.4. Concomitant Medications

Concomitant medications will be recorded from the time of consent until the subject's completion of the study. All concomitant medications, whether prescription or non-prescription (including pharmacological doses of vitamins), with the exception of medications listed below, are to be recorded in the eCRF by their generic name. The following medications DO NOT need to be recorded in the eCRF:

Standard medications and IV fluids typically required for sedation, induction, and maintenance of anesthesia during oocyte retrieval.

8.3. Efficacy Assessments and Procedures

8.3.1. Serum pregnancy/βhCG

A blood serum βhCG test must be obtained 10-14 days after blastocyst transfer. If the test is positive according to the local laboratory's reference ranges, this confirms a positive βhCG. In case of a doubtful / inconclusive βhCG result, a second test will be performed, preferably within 2 days.

8.3.2. Pregnancy Ultrasound

Clinical pregnancy will be defined as the presence of at least one intrauterine gestational sac by transvaginal ultrasound at approximately 4-6 weeks gestation.

Ongoing pregnancy will be based on detection of at least one intrauterine viable fetus by transvaginal or transabdominal ultrasound at 12 weeks gestation or later, with a detected fetal heartbeat considered normal and healthy and measured via ultrasound. "Normal" will be determined as expected for the gestational age ranging from 110 bpm to 180 bpm.

The patient will be required to obtain a week 20-24 Anomaly Scan ultrasound with their OBGYN clinician and will provide the full report at a second trimester visit for input into the CRF.

8.3.3. Pregnancy Outcome

Outcomes of pregnancy and birth data such as date and number/method of deliveries and birth weight will be recorded on the pregnancy outcome form. Complications of pregnancy, such as but not limited to: preterm labor, intrauterine fetal demise, preeclampsia/hypertension, bleeding/abruption, gestational diabetes, low birth weight, NICU admissions, as well as neonatal complications, will be reported. The patient will be required to obtain a newborn exam report within the first week of life from a licensed pediatrician and provide that report for input into the CRF.

8.3.4. Number and Size of Follicles during Stimulation

Transvaginal ultrasound will be performed at start of stimulation Day 2, Day 7 and 9 or 10 during the ovarian stimulation period to count and measure the number of follicles. All follicles over 3mm will be recorded separately for the right and left ovary.

8.3.5. Number and Distribution of Oocytes Retrieved

The number of oocytes retrieved will be recorded at the oocyte retrieval visit. The number of degenerated or non-cultured oocytes at retrieval will be recorded. The number of COCs cultured per droplet will be recorded in the eCRF as part of the study.

8.3.6. Metaphase II Oocytes

After the 30 hour culture, the oocytes will be stripped and evaluated for maturation. The number of metaphase II (M2) oocytes will be measured as defined by the presence of a first polar body (PB). The number of immature germinal vesicle (GV) oocytes will be measured, defined as lacking a PB and containing a germinal vesicle in the cytoplasm. The number of immature metaphase I (M1) oocytes will be measured, defined as lacking a PB and lacking a germinal vesicle. The Number of degenerated oocytes will be measured, defined as an abnormally shrunken, enlarged, darkened appearance indicating gamete death.

8.3.7. Number of Fertilized Oocytes and Fertilization Rate

After 16 to 18 hours post-ICSI, oocytes will be assessed visually for the presence of two pronuclei (2PN) and two polar bodies, defined as fertilized. Oocytes with a single polar body or no pronuclei will be considered non-fertilized and discarded. Oocytes with 1 or greater than 2 pronuclei will continue to be cultured separately from oocytes with 2 pronuclei.

8.3.8. Embryo Development

<u>Number and Quality of Embryos on Day 3</u>

Each embryo will be evaluated on day 3 after insemination. The quality evaluation will consist of assessment of cleavage stage and embryo morphology parameters (blastomere uniformity, degree of fragmentation and visual signs of multinucleation).

Cleavage stage will be defined by the number of blastomeres: 1, 2, 3, 4, 5, 6, 7, 8.

Blastomere uniformity will be classified as equally sized blastomeres or unequally sized blastomeres (largest blastomere >25% larger in average diameter compared to the smallest blastomere).

Degree of fragmentation will be classified as one of the following: 0%, 1-10%, 11-20%, 21-50% or >50% fragmentation, or totally fragmented (no blastomeres recognized).

Visual sign of multinucleation will be evaluated as yes or no.

<u>Number and Quality of Blastocysts on Day 5-7</u>

The quality evaluation of blastocysts on day 5-7 after oocyte retrieval will consist of assessment of three parameters: blastocyst expansion and hatching status, blastocyst inner cell mass grading, and trophectoderm grading. The scoring is based on the classification system by Gardner & Schoolcraft, with the addition of D-categories for inner cell mass and trophectoderm.

Blastocyst expansion and hatching status will be assessed as one of the following:

1. An early blastocyst, blastocoel being less than half volume of that of the embryo.
2. A blastocyst with a blastocoel whose volume is half of, or greater than half of, that of the embryo.
3. A blastocyst with a blastocoel completely filling the embryo.
4. An expanded blastocyst with a blastocoel volume larger than that of the early embryo, with a thinning zona.
5. A hatching blastocyst with the trophectoderm starting to herniate through the zona.
6. A hatched blastocyst, in which the blastocyst has completely escaped from the zona.

For blastocysts with expansion and hatching status 3-6, blastocyst inner cell mass grading and trophectoderm grading will be evaluated.

Blastocyst inner cell mass grading will be assessed as one of the following:

A. Tightly packed, many cells.
B. Loosely grouped, several cells.
C. Very few cells.
D. Degenerative or no inner cell mass.

Trophectoderm grading will be assessed as one of the following:

A. Many cells forming a cohesive epithelium.
B. Few cells forming a loose epithelium.
C. Very few, large cells.
D. Degenerative or very large cells.

Blastocysts with expansion and hatching status 3-6 will have a score combining the 3 parameters (blastocyst expansion and hatching status, inner cell mass, and trophectoderm); e.g., 4AB for a blastocyst with blastocyst expansion and hatching status 4, inner cell mass grading A, and trophectoderm grading B.

In the event of continued culture, blastocyst grading will be recorded after day 5.

8.3.9. Blastocyst for Frozen embryo transfer

Blastocyst survival after cryopreservation will be assessed for all thawed blastocysts at 0h (+0.5h) after thawing. Furthermore, re-expansion will be assessed for all survived blastocysts at 2.5h (±0.5h) after thawing.

8.4. Safety Assessments and Procedures

All adverse events will be recorded from the time of signed informed consent for participation in the trial until up to 6 weeks post-partum or early discontinuation.

Adverse events of special interest will be recorded for all subjects with an ongoing pregnancy.

For each adverse event the following parameters are recorded by the investigator: description of event, date of onset, intensity, causal relation to study intervention, action taken, other actions taken, seriousness of the adverse event, date of outcome, and outcome. Definitions of adverse events are provided in section 8.5.

OHSS: All cases of OHSS will be reported as adverse events with further details on signs and symptoms recorded on a specific OHSS AE form. Golan's classification system will be used for grading of each OHSS case as mild, moderate or severe.

Pregnancy outcome: All pregnancy and birth outcome data will be recorded on the pregnancy outcome form and AE or SAE form when applicable. Outcomes from NIPT and second trimester anomaly scan will be input to the CRF. Outcomes of pregnancy and birth data such as date and number/method of deliveries and birth weight will be recorded on the pregnancy outcome form. Complications of pregnancy, such as but not limited to, preterm labor, intrauterine fetal demise, preeclampsia/hypertension, bleeding/abruption, gestational diabetes, low birth weight, NICU admissions, etc. and birth (including neonatal complications) will be reported.

Technical problems with the intervention or control: The only possible technical problem with intervention would be loss of cells during preparation which is visualized during plate preparation. There are no anticipated technical problems with the control.

In case of technical malfunction that results in a replacement of a vial, all relevant details (including time, date, a description of the malfunction) of the incidence should be reported in the eCRF, the vial should be replaced and the participate continued. Human errors such as misunderstanding of instructions or incorrect handling of the intervention should not be regarded as technical malfunctions.

8.5. Adverse Events and Serious Adverse Events

8.5.1. Definitions of AE and SAE

An adverse event (AE) is any untoward medical occurrence associated with the use of a Investigational Product in humans, regardless of relationship to the Investigational Product. An AE could, therefore, be any unfavorable and unintended sign, symptom or disease temporally associated with the use of an Investigational Product, regardless of whether it is considered related to the Investigational Product. All AEs, including observed or volunteered problems, complaints or symptoms, are to be recorded on the appropriate eCRF. Each AE is to be evaluated for duration, intensity and causal relationship with the Investigational Product or other factors.

An SAE is defined as an AE that meets any of the criteria listed in the following table. SAEs will be collected for female subjects after informed consent until 30 days following the discontinuation of subject or completion of the final visit to confirm ongoing pregnancy or until the time of live birth for subjects with an ongoing pregnancy.

An event is defined a serious adverse event if it:	**Guidance**
results in death	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends, defined as up to 6 weeks postpartum, and irrespective of the causal relationship to the Investigational Product. The death of a subject enrolled in a study is per se not an event, but an outcome.
is life-threatening	The term "life-threatening" refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient hospitalization or prolongation of existing hospitalization	The term "hospitalization" means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e., if the case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before study inclusion are not considered AEs, if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
results in persistent or significant disability/incapacity	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgment by the Investigator.
is a congenital anomaly/birth defect	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the Product.

8.5.2. Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be monitored in the female subjects following informed consent until up to 6 weeks postpartum or until early discontinuation from the study. Adverse events of special interest will be monitored until live birth for subjects with an ongoing pregnancy at the final visit.

Serious adverse events will be monitored in the female subject following informed consent until early discontinuation or live birth.

8.5.3. Identifying AEs and SAEs

It is the responsibility of the Investigator to collect all AEs, both serious and non-serious, derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questioning (such as, “How do you feel?”).

AEs reported by the subjects as intermittent events are to be recorded on the eCRFs as one event with the start and stop date corresponding to the overall duration of the intermittent events and the severity reported as the highest severity reported during the intermittent events. Events are considered intermittent if the time period between distinct events was less than 48 hours; otherwise these are to be recorded as separate events.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms is to be recorded by the Investigator. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE.

Abnormal laboratory findings or other abnormal assessments that are judged by the Investigator as clinically significant are to be recorded as AEs, or SAEs if they met the criteria for a SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during or following ovarian stimulation, or were present at baseline and significantly worsened after screening are to be reported as AEs or SAEs.

8.5.4. Recording of AEs and SAEs

The Investigator must rate the severity (intensity) of each AE as mild, moderate, or severe, and to categorize each AE regarding its potential relationship to the Investigational Product using the categories of Related (causally related to the Investigational Product under study) and Not Related (unrelated to the Investigational Product under study).

Severity

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating, with inability to work or do usual activity.

8.5.5. Causality Assessment

The Investigator is responsible for assessing the causal relationship between an AE and the Investigational Product based on the available information.

In assessing this relationship, the Investigator should consider the potential etiologies for the observed AE. An AE may have been related to:

- the Product
- concomitant medications
- underlying disease pathology
- a pre-treatment condition
- a procedure performed in the course of the study
- another reason

Among the potential etiologies, the Investigator must decide, based on the most likely causal relationship, whether they consider the AE to be related or unrelated to the Investigational Product. The causality assessment provided for an SAE must be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations and the results of other diagnostic procedures.

8.5.6. Unexpected Adverse Events

An unexpected AE is any AE, the specificity or severity of which is not listed in the current protocol, that has not been previously observed with use of the Product.

8.5.7. Pregnancy Outcomes

All pregnancy and birth outcome data will be recorded on the pregnancy outcome form and AE/SAE form when applicable. Outcomes of pregnancy and birth data such as date and number/method of deliveries and birth weight will be recorded on the pregnancy outcome form. Complications of pregnancy, such as but not limited to, preterm labor, intrauterine fetal demise, preeclampsia/hypertension, bleeding/abruption, gestational diabetes, low birth weight, NICU admissions, etc. and birth (including neonatal complications) will be reported as AEs or SAEs when applicable.

8.5.8. Follow-up of AEs and SAEs

During the trial, the Investigator must follow-up on each AE/SAE until it is resolved or until the medical condition of the subject is stable. Evidence of aneuploidies from NIPT testing will be followed up by confirmatory testing as indicated. For congenital abnormalities identified by a pediatrician, a referral to a clinical geneticist or neonatologist will be made for further evaluation.

After the subject's last visit, the Investigator must follow-up on any AE classified as serious or considered to have a reasonable possible causality to the study treatment until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Gameto.

8.5.9. Reporting of SAEs

All SAEs must be reported immediately to Gameto as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details within 3 calendar days of his/her knowledge of the SAE.

The SAE Report Form must be completed and submitted according to the instructions provided on the form.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters, invasive procedures, scans and x-rays, and autopsy results can be scanned and e-mailed to Gameto using the contact details on the form. In any case this information must be supplied by the investigator upon request from Gameto. On any copies provided, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Gameto and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Gameto will report SAEs according to local regulations.

8.5.10. Follow-Up Reports

Detailed information should be entered when follow-up information becomes available. The Investigator is required to continue to follow the subject until either the SAE is resolved, the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

8.5.11. Serious and Unexpected Adverse Reaction Reporting

In case of Suspected (means with a possible causal relationship) Unexpected Serious Adverse Reaction (SUSAR) to the study intervention, an Expedited Reporting to Health Authorities and Ethic Committees by Gameto is required, so that the Investigator must collect to the fullest the information regarding the SUSAR, after evaluating the primary care to be delivered to the subject to preserve at first their health status. In case of a SUSAR requiring unblinding for serious safety reasons (a life-threatening/fatal condition), the Investigator must immediately open the emergency code and proceed with the most appropriate treatment. Should this happen, the Investigator must promptly inform Gameto within 24 hours from its occurrence.

- Fatal or life-threatening SUSARs should be reported by Gameto to concerned Health Authorities and Ethic Committees as soon as possible but not later than 7 calendar days from Gameto's first knowledge, followed by a follow-up report as complete as possible within 8 calendar days.

- All the other SUSARs must be notified by Gameto to Health Authorities within 15 calendar days.

Relevant follow up information must subsequently be communicated within an additional 15 days.

The clock for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by Gameto.

8.5.12. Adverse Events of Special Interest

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms using a classification system based on Golan's classification system as shown in the table below.

Classification of OHSS Symptoms

OHSS stage	Clinical feature	Laboratory feature
Mild	Abdominal distension/discomfort Mild nausea/vomiting Mild dyspnea Diarrhea Enlarged ovaries	No important alterations
Moderate	Mild features Ultrasonographic evidence of ascites	Hemoconcentration (Hct > 41%) Elevated WBC (> 15,000 mL)
Severe	Mild and moderate features Clinical evidence of ascites Hydrothorax Severe dyspnea Oliguria/anuria Intractable nausea/vomiting Low blood/central venous pressure Pleural effusion Rapid weight gain (> 1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis	Severe hemoconcentration (Hct > 55%) WBC > 25,000 mL CrCl < 50 mL/min Cr > 1.6 mg/dL Na+ < 135 mEq/L K+ > 5 mEq/L Elevated liver enzymes
Critical	Anuria/acute renal failure Arrhythmia Thromboembolism Pericardial effusion Massive hydrothorax Arterial thrombosis Adult respiratory distress syndrome Sepsis	Worsening of findings

WBC = white blood count; OHSS = ovarian hyperstimulation syndrome

8.5.13. Pregnancy Loss

The following terminology should be used for reporting of pregnancy losses as adverse events:

Biochemical pregnancy loss: Positive βhCG test but all intrauterine gestational sacs are absent or without fetal heart beat as documented by

	ultrasound, or there are no viable fetuses observed by ultrasound
Ectopic pregnancy:	Extrauterine gestational sac with or without fetal heart beat as documented by ultrasound or surgery
Clinical miscarriage:	Loss of clinical pregnancy up to 12 weeks gestation
Late clinical miscarriage:	Loss of clinical pregnancy after 12 weeks gestation

8.5.14. Pregnancy Complications

The following data will be collected via in person visit of all subjects with an ongoing pregnancy with a Yes or No at approximately 20-24 weeks gestation and live birth: Did you experience any of the following? hypertensive disorders of pregnancy (hypertension, pre-eclampsia, and eclampsia, HELLP syndrome), antepartum hemorrhage, gestational diabetes mellitus. If yes, additional adverse event data will be collected. Additionally, a week 20-24 Anomaly Scan, performed by the subject's OBGYN and a newborn exam performed within the first week of life by the subject's pediatrician will be provided. A comprehensive record review including all prenatal and birth records, obtained directly from the treating providers (e.g., Obstetrics and Pediatrics) will be performed and input into the CRF for assessment of developmental abnormalities in the second trimester. For this record review, the study investigator will review all prenatal and pediatrician records through 6 weeks post-partum at a time later than 6 weeks post-partum.

8.5.15. Serious Adverse Events during Post-trial Activities

Pregnancy outcome will be gathered for all subjects with an ongoing pregnancy. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth. These data will be reported via acquisition of a newborn exam report, conducted by a licensed pediatrician within the first week of life.

The following untoward medical occurrences reported as part of this post-trial follow-up information will be recorded as SAEs:

- Death of mother in connection with pregnancy or labor
- Death of neonate / infant
- Stillbirth
- Neonate admitted to the neonatal intensive care unit (NICU) regardless of duration
- Congenital anomaly / birth defect
- Medically important event

In case of admission to NICU, the reason for admission must be reported as an SAE, rather than just the act of hospitalization. In the case of an identified congenital abnormality, a follow up with be conducted with an appropriate physician and results will be collected.

Additionally, as part of post-trial activities, patients reporting a live birth will be consented to enroll in a Fertilo infant follow up registry. The registry will be established directly with the patient and be included as a discrete database study as part of post-trial and post-market surveillance activities. For this registry, email communication will be sent to the mother to collect pre-defined measures of infant health for a 2-year postnatal period. At the conclusion of the live birth collection, patients will sign consent to participate in the 2-year follow-up registry. Participants will be sent a link via email to sign up and answer questions regarding the health of the child. The Sponsor will send a detailed questionnaire at 6 months, 1 year, and 2 years post-birth with a series of questions regarding key health metrics. If the participant answers yes to any of the questions they will be contacted to request additional information for collection and reporting.